# EPA Office of Pesticide Program's Initiative to Modernize the Acute "6-Pack"

Society of Toxicology
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# Submitted Acute 6-Pack Studies

| | Guideline | 2012 | 2013 | 2014 | 2015 |
|---|---|---|---|---|---|
| **Acute oral** | 870.1100 | 324 | 248 | 328 | 268 |
| **Acute dermal** | 870.1200 | 292 | 257 | 313 | 255 |
| **Acute inhalation** | 870.1300 | 264 | 217 | 248 | 254 |
| **Eye irritation** | 870.2400 | 291 | 261 | 273 | 251 |
| **Skin irritation** | 870.2500 | 270 | 254 | 268 | 258 |
| **Skin sensitization** | 870.2600 | 247 | 237 | 262 | 267 |

# Acute Toxicity “6 Pack”

- Letter to Stakeholders on OPP’s Goal to Reduce Animal Testing from Jack E. Housenger, Director.
  - https://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2016-0093-0003
  - Working in partnership with other governmental entities, industry and non-governmental organizations (NGOs) and need continued robust participation and support to achieve our mutual goal.
  - Activities fall under three main objectives
    - Critically evaluating which studies form the basis of OPP decisions;
    - Expanding acceptance of alternative methods and;
    - Reducing barriers such as challenges of data sharing among companies and international harmonization to adopting alternative methods in the U.S. and internationally.

| TEST | ALTERNATIVE TEST | OECD |
|---|---|---|
| **Skin Irritation** | Reconstructed Human Epidermis models | OECD TG 431 |
| | Reconstructed Human Epidermis models | OECD TG 439 |
| **Eye Irritation** | Bovine corneal opacity permeability (BCOP) test | OECD TG 437 |
| | Transcutaneous Electrical Resistance Test Method (TER) | OECD TG 430 |
| | Fluorescein Leakage | OECD TG 460 |
| | Isolated chicken eye (ICE) test | OECD TG 438 |
| | Reconstructed human Cornea-like Epithelium (RhCE) | OECD TG 492 |
| **Skin sensitization** | Direct Peptide Reactivity Assay (DPRA) | OECD TG 442C |
| | Keratinosens assay | OECD TG 442D |
| | Human Cell Line Activation Test (h-CLAT) | OECD TG 442E |

# U.S. Federal Collaboration

- In 2000, Congress passed the ICCVAM Authorization Act and established Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)
  - Comprised of 16 Federal regulatory and research agencies that require, use, generate, or disseminate toxicological and safety testing information.
- NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) of the NIEHS provides scientific and operational support for ICCVAM technical evaluations and related activities.
- Work in collaboration with Acute Systemic, Eye/Skin Irritation & Skin Sensitization Technical Workgroups


Agency for Toxic Substances and Disease Registry • Consumer Product Safety Commission • Department of Agriculture
Department of Defense • Department of Energy • Department of the Interior • Department of Transportation
Environmental Protection Agency • Food and Drug Administration • National Institute for Occupational Safety and Health
National Institutes of Health • National Cancer Institute • National Institute of Environmental Health Sciences
National Library of Medicine • Occupational Safety and Health Administration • National Institute of Standards & Technology

# Developing database of acute toxicity data from pesticide products

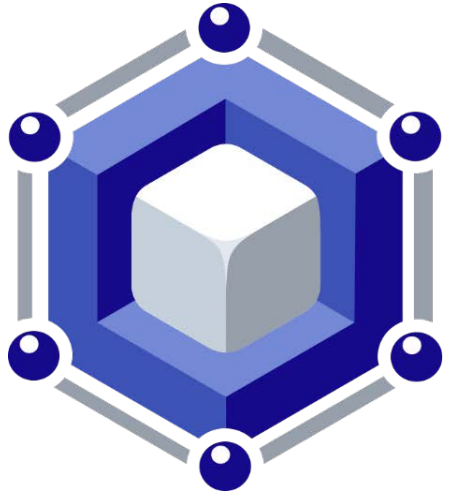
- Collaborative effort between EPA & NICEATM, as part of charge for ICCVAM Acute Toxicity Workgroup
- Purpose:
  - Assess variability within and across studies  for comparing/evaluating to alternative approaches
  - Develop read across approaches
  - Assess GHS additivity equation
- Study protocol components: strain/species/dosing route/testing laboratory, sex, concentration/particle size
- Acute oral, dermal and inhalation toxicity data and skin sensitization have been extracted; data curation is still on-going
- Data extraction for skin/eye irritation in progress

# Collaborations: Tools for Risk Assessors

## Integrated Chemical Environment

- User-friendly access point for high quality data and reference chemical lists
- Enable wider community (regulators) to engage in the use computational approaches for assessing chemical safety
- Flexible, exportable results
  - Both in computer-friendly format and a human-friendly summary format
- Initial Launch: March 2017, SOT annual meeting
- Database of pesticide acute 6-pack data expected to be released in ICE around October, 2017

NTP
National Toxicology Program



Integrated
Chemical
Environment

# Acute Toxicity “6 Pack”

- Acute Dermal Pesticide Formulation Toxicity Testing
  - Collaboration between EPA & NIEHS-NICEATM
  - Analyze the relative contribution of data from acute oral and dermal toxicity tests to pesticide hazard classification and labelling
  - Collected acute lethality dermal and oral toxicity data from rat studies with pesticide formulations
    - Dataset ~600 different formulations across >200 active ingredients.
  - *Final document published: Waivers being granted.*

# Steps Towards Adopting Non-Animal Methods

- We have started a voluntary pilot program where registrants may send the *in vivo* acute lethality study for oral and inhalation formulation/product testing as currently required and simultaneously submit the calculations using the GHS dose additive mixtures equation.
  - Hope to rapidly collect a dataset evaluating the ability of the GHS mixtures equation to predict the acute toxicity categories from oral and inhalation routes in formulation/product testing.
  - Pending the outcome of that analysis, may be able to substantially reduce the use of animals.

# Steps Towards Adopting Non-Animal Methods

- GHS additivity formulas for classifying formulations and mixtures for the acute toxicity

The acute toxicity estimate (ATE) of ingredients should be considered as follows:

- Include ingredients present at 1% or greater with a known acute toxicity, which fall into any of the GHS acute toxicity categories.
- Ignore ingredients that are presumed not acutely toxic (e.g., water, sugar).
- Ignore ingredients if the oral limit test does not show acute toxicity at 2,000 mg/kg/body weight.

The ATE of the mixture is determined by calculation from the ATE values for all relevant ingredients according to the following formula below for Oral, Dermal or Inhalation Toxicity:

$$\frac{100}{ATE_{mix}} = \sum_{\eta} \frac{C_i}{ATE_i}$$

where:
$C_i$= concentration of ingredient i
n ingredients and i is running from 1 to n
$ATE_i$ = Acute Toxicity Estimate of ingredient I

# International Cooperation on Alternative Test Methods (ICATM)

- Representatives from: USA, EU, Japan, Korea, Canada, Brazil, China
  - First ever ICATM Workshop, October 4-5, 2016 in Ispra, Italy
  - On the international regulatory applicability and acceptance of alternative non-animal approaches
    - Identify the current regulatory requirements for skin sensitization in different regions by chemical sector (i.e. pesticides, cosmetics, pharmaceuticals, industrial chemicals, etc.);
  - More than >20 regulatory authorities were represented.
  - Identify what obstacles hamper the use of non-animal approaches in certain regulatory areas and regions;
  - Aim to achieve agreement on acceptance of skin sensitization IATAs;
    - Consider the ICCVAM IATA and others submitted to OECD
  - Define a set of performance based criteria for acceptance of future testing strategies.

# International Cooperation on Alternative Test Methods (ICATM)

- Multiple non-animal testing strategies incorporating *in vitro, in chemico*, and *in silico* inputs demonstrate *comparable or superior performance* to the LLNA.
- A planned product of the ICATM workshop is the development of an assessment framework for integrated non-animal approaches that could *serve as replacements* for the current animal test, the LLNA.
- Publications in the scientific literature and white papers are likely to be developed based on the outcomes of the workshop.
  - SPSF already submitted to OECD---jointly sponsored by US, Canada, EU
- NTP conducting prospective testing for 3 different assays to fill in gaps for chemical sector & formulations/mixtures

# Alternative Assays:  Eye Irritation

- Currently have a policy in place to accept eye irritation assays for antimicrobial cleaning products
- Interested in extending use of alternative assays for other classes of pesticides
- Voluntary data collection effort for conventional pesticides
  - >200 pairs of *in vitro-in vivo* data provided by industry
- NICEATM is analyzing these new data in combination with the data from the antimicrobial cleaning product policy
  - Data entry is complete, analysis is on-going
  - Some prospective testing to fill in gaps may be needed

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# Questions?